Statistical evaluation of the bootstrap estimate of spatial intensity of disease cases when using quadrat samples

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Abstract: *The aim of the present work is to investigate the performance of the method bootstrap for estimating the sampling distribution of intensity of disease cases located in different geographical areas when sampling is made through cases located in a sample of square area. Simulated data from a design factorial experiment were applied to study the effects of type of pattern, number of quadrats, number of quadrats sampled, number of bootstrap samples and number of events in the pattern on the bootstrap confidence intervals for spatial intensity. It was observed that the bootstrap estimate of the standard error and consequently of the confidence interval for spatial intensity depends on all the main factors except for the number of bootstrap samples. The performance of the method bootstrap was dubious to estimate sampling distribution for spatial intensity when the sampling is based on a sample of quadrats. These results can help the public health planners with results about estimates of the number of disease cases in a geographical area, starting from a sample of locations of cases within specific regions.*

Key words: *bootstrap, spatial point patterns, spatial intensity, disease location*

Resumo: *O objetivo do presente trabalho é investigar o desempenho do método* bootstrap *para estimar a distribuição amostral da intensidade de casos de doenças localizadas em diferentes áreas geográficas quando se utiliza contagem de casos localizados em uma amostra de áreas quadradas. Dados simulados de um experimento fatorial planejado foram aplicados para estudar os efeitos de tipo de configuração espacial, número de quadrados, número de* *quadrados na amostra, número de amostras* bootstrap *e número de eventos na configuração nos intervalos de confiança* bootstrap *para a intensidade espacial.*

Foi observado que a estimativa bootstrap *do erro padrão e, conseqüentemente, do intervalo de confiança para a intensidade espacial dependem de todos os fatores analisados com exceção do número de amostras* bootstrap.

A performance do bootstrap *foi duvidosa para estimar intensidade espacial baseada em uma amostra de quadrados. Estes resultados podem ajudar os planejadores da área de saúde pública com resultados sobre estimativas do número de casos de doença em uma área geográfica, a partir de uma amostra de casos localizados dentro de regiões específicas.*

Palavras-chave: bootstrap, *configurações de padrões espaciais, intensidade espacial, localização de doenças*

1 Introduction

The use of maps and the concern with the geographical distribution of diseases are very old. The Scottish naval surgeon James Lind published in 1768 a book called *An Essay on Diseases Incidental to Europeans in Hot Climates* in which he seeks explanations for the distribution of diseases, considering risks to certain specific geographical areas. Ever since, several works have been written in the field of geographical epidemiology, describing area variations in the distribution of disease cases (e.g. BARRET, 1999; CHRISTMAN, 2000; LAWSON *et al.*, 1999; SNOW, 1854). It stands out, among others, the study of SNOW (1854) that used mapping techniques to relate the cases of cholera and points of collection of water in the center of London during the nineteenth century.

In a first approach to the study of the geographical distribution of diseases, each case can be idealized as a point and a set of n point locations, distributed by a stochastic process within some study region R, can be considered a spatial point pattern.

The analysis of a spatial point pattern depends on the way in which the pattern is observed. If the pattern is represented by all the events (mapped), the null hypothesis of completely spatial randomness (CSR) can be tested and then, if the null hypothesis is rejected, a complete stochastic model can be fitted to represent the spatial distribution of the events. However, mapped data in public health can be difficult and expensive and therefore not feasible. In this case, one will have to use a sample of events of the region (sparse sampling) to drive the research. The first interest of the analysis of sparsely sampled point patterns is usually aimed at estimating the number of events (disease cases) within some specific region or, equivalently, the intensity, defined in the theory of spatial point patterns to be the mean number of events per unit area region. It is also possible to test the hypothesis of completely spatial randomness (e.g. DIGGLE, 1983).

A number of the so called sparse sampling methods (e.g. quadrat counts, kernel, line transects, distances) have been developed for estimating spatial intensity. DIGGLE (1983) and UPTON and FINGLETON (1985) provide a review of the advantages and disadvantages of these methods. Those authors advocate that the simplest one is the quadrat counts and therefore, we are assessing this method in the present work.

In quadrat counts, the number of events falling into each sample of small sub regions (called quadrats) are recorded. Thus, the estimate of the intensity is based on these records. In order to facilitate the interpretation of the quadrat counts method, one can imagine that the region of interest is a city where the quadrats are the blocks and the events are the location of the disease cases within the blocks.

Point estimates of intensity may be difficult to interpret without some idea of their accuracy. In the last years, a resampling method called bootstrap has been a popular tool for constructing confidence intervals in many branches of statistics, also for point patterns (e.g. EFRON and TIBSHIRANI, 1993). Indeed, some authors (e.g. BRAUN *et al.*, 1998; COWLING *et al.*, 1996; SNETHGALE, 1999) have developed statistical procedures using bootstrap techniques. All these papers deal with the accuracy of the intensity point estimation just for time point processes. CRESSIE (1993) points out that although there is a considerable overlap of methods for point processes occurring in space and for those occurring in time, it would be wrong to say that the results obtained in the temporal case can be applied directly to the space case.

We observe that very little work has been done on how well the bootstrap works in practice in spatial point patterns. HALL (1985) has investigated the possibility of resampling a spatial point pattern. He has suggested that resampling provide a unified and philosophically attractive approach to several problems of inference such as constructing confidence intervals. SOLOW (1989) has proposed and illustrated the use of the bootstrap to estimate the sampling distribution of Bith's distance-based estimator of intensity. SOLOW (1989) showed that the bootstrap performed fairly well in estimating that distribution.

The drawback of HALL′s (1985) study is that he has evaluated the resampling methods through pure theoretical treatment. One limitation of SOLOW′s (1989) work is that he has evaluated the bootstrap method only through a particular data set. It is well known that an estimate of intensity depends on, among other factors, the type of the spatial point pattern (e.g. DIGGLE, 1983; UPTON and FINGLETON, 1985).

The main question is: Does the bootstrap sampling distribution of the spatial intensity also depend on these factors? Thus, for a proper evaluation of the bootstrap method, we require repeated application to independent random samples from the same populations in a vast range of conditions. Consequently, the results obtained by SOLOW (1989) cannot be applied directly in practical situations in geographical epidemiology. Thus, the main purpose of the present work is to investigate, through simulation from a design factorial experiment, how well the bootstrap performs in estimating the sampling distribution of the intensity of disease cases in different spatial point patterns.

2 Methods

A factorial design was conducted, as described in MONTGOMERY (1991), with five factors and two levels each factor, exclusively through simulation, to investigate the performance of the bootstrap for estimating intensity in sparsely sampled spatial point patterns.

The dependent variable of interest was the estimated standard error of spatial intensity. We have adopted a quadrat counts-based estimator of intensity, where the study region with area R is divided in c quadrats of equal size. Once the c quadrats have been positioned, in the next stage, it is chosen randomly q quadrats. Then, the number of events falling into each of the q quadrats is recorded $(i = 1, ..., q)$. In this case, the simplest analytical estimator of intensity, derived from DIGGLE (1983), is given by the expression

$$\widehat{\lambda} = \frac{\sum_{j=1}^{q} X_j}{(qR)/c} \tag{1}$$

UPTON and FINGLETON (1985) and LAWSON *et al.* (1999) point out that under the supposition that the disease cases are distributed at random, and therefore the observations come from a homogeneous Poisson process with parameter λ, the expression (1) is always an unbiased estimator for intensity, where its standard deviation is given, approximately, by the equation

$$S(\widehat{\lambda}) = \left(\frac{c^2 \sum_{j=1}^{q} X_j}{qR} \right)^{1/2} \tag{2}$$

An example of how to get an estimate of intensity and its standard deviation by using the quadrat counts method is presented in the Figure 1. We consider a sample of four quadrats at the corners with 7, 3, 7 and 4 events falling into each of the quadrats (marked) and therefore $q = 4$, $c = 9$, $R = 1$ and $\sum_{j=1}^{4} X_j = 21$. Thus, applying the expressions (1) and (2), one can get, respectively, estimates of intensity and standard deviation, approximately, equal to 47 and 20.62 events per unit square area.

In this work the main factors of interest (independent variables) are: *number of quadrats in the region* (QUA), *number of quadrats sampled* (SAM), *type of patterns* (PAT), *number of events within the patterns* (EVE) and *number of bootstrap samples* (DRA).

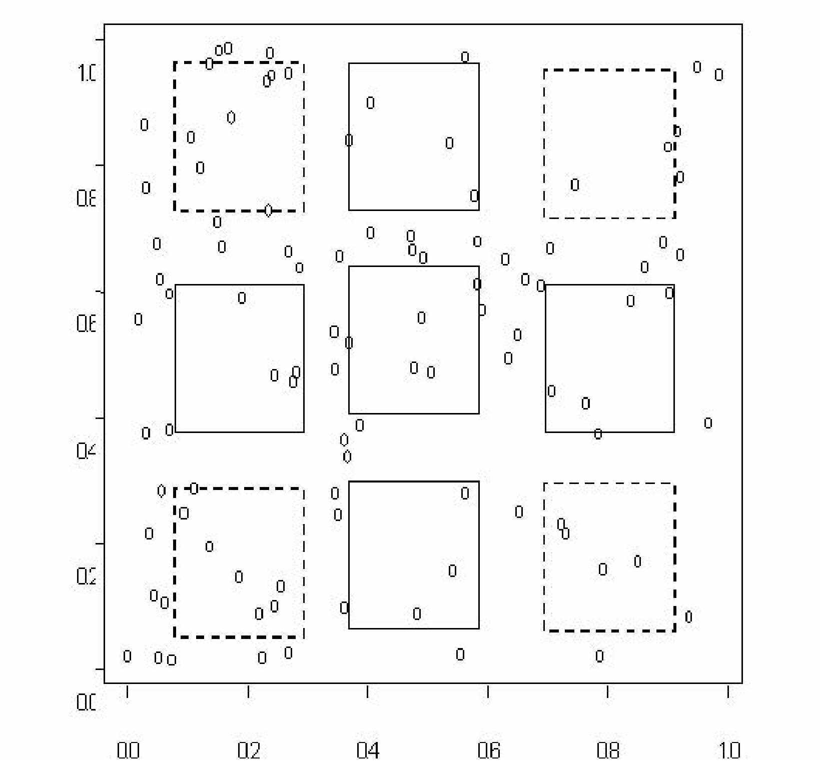

Figure 1. Quadrat counts method for estimating the spatial intensity in a homogeneous Poisson point pattern with 50 events within a unit square area.

To study the effect of the number of quadrats in the region, we used two levels (16 and 36 quadrats), while the effect of the number of quadrats sampled was studied by using the levels 8 and 12 samples.

To examine the influence of the factor type of pattern, we had also used two levels: the completely spatial randomness and cluster that represent common types of incidence of disease cases in geographical epidemiology. The completely spatial randomness (CSR), or the homogeneous Poisson process, is the basic model for the spatial configuration of events. We can say that the cases of diseases are randomly distributed within the region R with intensity λ, or equivalently, that the location of the events within a study region is a random sample of a uniform distribution. Observe that just one parameter λ is necessary to define the homogeneous Poisson process (e.g. CRESSIE, 1993; DIGGLE, 1983). In this work we have simulated CSR patterns with 25 or 100 events in a unit square area.

The Poisson cluster process (CLU) incorporates an explicit form of spatial clustering and assumes a mechanism in which events tend to group around each other. It suggests a formation of relatively dense sub-regions of events over the region R under consideration. More formally, we have a parent process P, usually a homogeneous Poisson process with intensity λ and a daughter process D. A sample of parent processes produces, independently, a random number of daughter processes with the same radial variability s. Each daughter process is, independently, spatially distributed relatively to the corresponding parent process. The cluster process may consist either of the superposition of the daughter process only or of the superposition of parent and daughter processes. Observe that it is necessary three parameters to define the Poisson cluster process: the intensity λ, the number of elements of the parental process P and the radial variability s of the distribution of the daughter process about of the paternal (e.g. CRESSIE, 1993; DIGGLE, 1983). In this work we have simulated cluster patterns with 25 or 100 events in a unit square area, 10 parents and radial variability equal to 0.05.

The last factor of interest was the number of bootstrap samples. The idea behind bootstrap is remarkably simple. In this method, new samples B, each of the same size as the observed original sample, are drawn, with replacement, from the observed original sample. The spatial intensity is first calculated using the observed original sample and then recalculated using each of the new samples (bootstrap samples), yielding a bootstrap distribution. This resulting distribution can be used to make inferences about the spatial intensity. One way of doing this is the development of confidence intervals around the spatial intensity, given both intensity and standard error estimates. There are several bootstrap methods available for constructing confidence intervals. In this work we are using the normal approximation method, in which the bootstrap estimates of the intensity and standard errors are the mean and the standard deviation of the B samples (e.g. EFRON and TIBSHIRANI, 1993). In this work we adopted B equal to 250 or 1000.

After selecting the number of levels for each factor, we run experiments with all possible combinations. In our case, we had two levels for all five factors and therefore, our 2×5 factorial design required 32 runs.

We now give an example of a particular run in our factorial design. For this, we have used the following combination: PAT = CSR; EVE = 100; QUA = 16; SAM = 8 and DRA = 250. The simulation work is as follows:

- STEP 1 - We simulated a CSR pattern with 100 events in a unit square area such as presented above.
- STEP 2 - The CSR pattern was divided in 16 quadrats with the same size.
- STEP 3- The number of events falling into each quadrat was recorded.
- STEP 4 - A sample of 8 quadrats was randomly chosen and their respective events were recorded.
- STEP 5 - Estimate of intensity was obtained by using the equation (1).
- STEP 6 - The bootstrap estimates of intensity and standard error were found by drawing randomly with replacement 250 times the original sample set obtained at step 4, where the bootstrap estimate intensity was given by the following

expression

$$\widehat{\lambda}_B = \frac{\sum\limits_{i=1}^{250} \widehat{\lambda}_i}{250} \tag{3}$$

while the bootstrap standard error was given by the following expression

$$SE = \left[\frac{\sum\limits_{i=1}^{250} \left(\widehat{\lambda}_i - \widehat{\lambda}_B \right)^2}{249} \right]^{1/2} \tag{4}$$

- STEP 7 - The 95% confidence intervals based upon the bootstrap (normal approximation method) can be obtained using the expression

$$\widehat{\lambda} \pm 1.96 \times SE \tag{5}$$

- STEP 8 - The simulation in steps 1 to 7 were repeated for each treatment combination until we had completed the 32 runs.

We applied the analysis of variance, as described in MONTGOMERY (1991), for estimating the main effects and two-factor interaction on the standard errors provided by the 32 runs of the factorial experiment. We used the function "*aov*", available in the software S-PLUS (1997), for carrying out such analysis.

3 Results

Table 1 shows the results of the simulation work from the 32 runs of the design factorial experiment where one can see that all real spatial intensity are included in the confidence intervals. The point estimates of intensity were also significantly positively related to the real intensity ($R = 0.96$, $P < 0.001$). By calculating the Pearson correlation coefficient (R) from the results presented in Table 1, we got that the two measures of variability (analytical and bootstrap) were significantly positively related ($R = 0.67$, $P < 0.001$).

RUN	QUA	SAM	EVE	DRA	PAT	$\widehat{\lambda}$	SD($\widehat{\lambda}$)	SE	IL	SL
1	16	08	100	250	CSC	110.00	41.95	13.95	82.65	137.34
2	16	12	100	250	CSC	94.67	38.92	12.85	69.48	119.86
3	16	08	25	250	CSC	28.00	21.17	3.95	20.26	35.74
4	16	12	25	250	CSC	22.67	19.04	3.07	16.65	28.69
5	16	08	100	1000	CSC	94.00	38.78	15.08	64.44	123.56
6	16	12	100	1000	CSC	97.33	39.46	13.10	71.65	123.01
7	16	08	25	1000	CSC	28.00	21.17	3.68	20.79	35.21
8	16	12	25	1000	CSC	25.33	20.13	3.54	18.39	32.27
9	16	08	100	250	CLU	98.00	39.60	46.94	5.99	190.00
10	16	12	100	250	CLU	96.00	39.19	35.93	25.58	166.42
11	16	08	25	250	CLU	20.00	17.89	10.39	0.36	40.36
12	16	12	25	250	CLU	28.00	21.17	9.21	9.95	46.05
13	16	08	100	1000	CLU	140.00	47.33	47.07	47.74	232.26
14	16	12	100	1000	CLU	78.67	35.48	33.30	13.40	143.93
15	16	08	25	1000	CLU	22.00	18.76	9.36	3.65	40.34
16	16	12	25	1000	CLU	25.33	20.13	9.91	5.91	44.75
17	36	08	100	250	CSC	84.00	54.99	10.37	63.67	104.32
18	36	12	100	250	CSC	100.00	60.00	12.06	76.36	123.64
19	36	08	25	250	CSC	28.00	31.75	6.82	14.63	41.36
20	36	12	25	250	CSC	25.33	30.20	5.48	14.59	36.07
21	36	08	100	1000	CSC	108.00	62.35	15.04	78.52	137.48
22	36	12	100	1000	CSC	90.67	57.13	11.55	68.03	113.31
23	36	08	25	1000	CSC	24.00	29.39	6.26	11.73	36.27
24	36	12	25	1000	CSC	17.33	24.98	3.87	9.74	24.91
25	36	08	100	250	CLU	122.00	66.27	55.84	12.55	231.45
26	36	12	100	250	CLU	94.67	58.38	38.97	18.29	171.05
27	36	08	25	250	CLU	24.00	29.39	12.68	-0.85	48.85
28	36	12	25	250	CLU	30.67	33.23	13.58	4.05	57.29
29	36	08	100	1000	CLU	128.00	67.88	58.14	14.04	241.95
30	36	12	100	1000	CLU	108.00	62.35	39.44	30.69	185.30
31	36	08	25	1000	CLU	34.00	34.99	16.76	1.15	66.89
32	36	12	25	1000	CLU	33.33	34.64	12.24	9.34	57.32

Table 1 - Point estimates of intensity (λ), standard deviations (SD), standard errors (SE), inferior limits (IL) and superior limits (SL) for 95% bootstrap confidence intervals for spatial intensity from the 2×5 design factorial experiment. The main factors are: number of quadrats in the region (QUA); number of quadrats sampled (SAM); type of patterns (PAT); number of events within the patterns (EVE) and number of bootstrap samples (DRA).

Table 2 summarizes the results of the analysis of variance for the estimates of both intensity and standard error where we can see that all main factors are statistically significant on the estimate of the standard deviation. Table 2 also shows that all main factors, except the number of bootstrap samples from the available quadrats, are statistically significant on the bootstrap estimate of the standard error. There are also many second-order interactions statistically significant on both estimates.

Source of	Standard deviation		Standard error	
variation	F	P	F	P
QUA	248.853	< 0.001	7.590	0.014
SAM	3.010	0.097	18.569	< 0.001
EVE	605.429	< 0.001	364.402	< 0.001
DRA	–	–	0.131	0.721
PAT	4.659	0.042	321.964	< 0.001
QUA×SAM	0.223	0.641	0.779	0.390
QUA×EVE	23.692	< 0.001	0.006	0.936
QUA×DRA	–	–	0.258	0.618
QUA×PAT	5.242	0.032	6.321	0.023
SAM×EVE	2.097	0.162	10.655	0.005
SAM×DRA	–	–	0.723	0.407
SAM×PAT	0.137	0.714	10.183	0.005
EVE×DRA	–	–	0.097	0.759
EVE×SAM	0.415	0.526	127.058	< 0.001
DRA×PAT	–	–	0.003	0.959

Table 2 - Results of the analysis of variance (F-statistics and P-values) of the standard deviation and bootstrap standard error versus the main factors: number of quadrats in the region (QUA); number of quadrats sampled (SAM); type of patterns (PAT); number of events within the patterns (EVE) and number of bootstrap samples (DRA). The symbol "×" means interaction between the two main factors. The symbol " – " means that the value is not available.

4 Discussion

The purpose of the present work was to investigate, through simulation, how well the bootstrap method performs estimating sampling distribution of the spatial intensity of disease cases in a particular geographical region. The estimate of the intensity of disease cases in a region can be useful in those cases where the epidemiologist needs to know the number of cases occurring in a region based just on a sample of disease cases. Although there are many procedures available for estimating point intensity, such as angle-count, areal, kernel, line transects and distance based methods (e.g. UPTON and FINGLETON, 1985), we focused our work on quadrat counts because some authors, such as CHRISTMAN (2000), CRESSIE (1993), DIGGLE (1983), LAWSON *et al.* (1999) and UPTON and FINGLETON (1985) advocate that this method is the simplest and therefore, the most popular for point estimate of intensity in sparsely sampled spatial point patterns.

First of all, one may be interested in knowing whether the bootstrap is capable for predicting correctly the real spatial intensity. We have observed an almost perfect positive relationship between the point estimates of intensity and the real intensity ($R = 0.96$, $P < 0.001$). Table 1 also shows that all real spatial intensity is included in the 95% bootstrap confidence intervals. Thus, there is no reason to be afraid of the method.

We know that all analytical expression available for the standard error of intensity depends on the intensity, type of pattern, total area of the quadrats as well as the size of the used quadrats (e.g. CHRISTMAN, 2000; UPTON & FINGLETON, 1985). Another way to get the variability of the estimates is through the sampling distribution of the estimators. In this work, we have suggested the use of bootstrap, which is non-parametric, since it is not necessary to specify a model of the underlying spatial process.

One may be also interested in knowing whether there is a relationship between bootstrap and analytical methods for variability estimates. We used the Pearson correlation coefficient (R) to examine the possibility of such relationship. Although we observe (Table 1) a positive relationship between the two estimates (analytical and bootstrap) ($R = 0.67$, $P < 0.001$), the bootstrap leads to smaller variability measures than the analytical method. Thus, the bootstrap can provide more precise estimates than the analytical method.

A simulation-based design factorial experiment was used to answer more specific questions: What are the main factors that affect both the bootstrap standard errors and standard deviation of intensity? Do the factors act independently on the estimates? We observe that the use of a factorial experimental design is a novel approach for assessing the effectiveness of that sampling distribution.

The analysis of variance (Table 2) shows that the number of events in the pattern effect is statistically significant ($P < 0.001$). We observe that the larger the number of events in the pattern, the bigger is the standard error, that is, the variability is directly proportional to the intensity of disease cases. The factor number of quadrats seems to be statistically significant and therefore there is quadrat size effects in the bootstrap estimates ($P < 0.001$). The results showed sampling area effect ($P = 0.073$) on the bootstrap estimates. The analysis of variance showed that the bootstrap estimator is directly linked to the identification of the patterns ($P < 0.001$). Actually, the bootstrap estimator tended to provide larger values of standard errors in cluster patterns than in random patterns. Thus, it is always a good idea to perform a test against the hypotheses of randomness before estimating intensity. For a review of the methods available for testing against spatial randomness, one can see CRESSIE (1993) and DIGGLE (1983). As we expected, the number of bootstrap samples was not statistically significant for estimating intensity because we used 250 and 1000 samples drawing in our experiment. These numbers are compatible with EFRON and TIBSHIRANI (1993) suggestions. They argue that replications equal 50 is often enough to give a good estimate. Very seldom are more than 200 replications needed to estimate the standard error. Much bigger replications (between 200 and 1000) are required for the bootstrap confidence intervals.

The analysis of variance showed that both estimators (analytical and bootstrap) tended to provide, in general, the same statistically significant results. Thus, these results show that there is no need to carry out bootstrap, as the analytical estimator leads to results which can be obtained simplier without simulation.

Even though the performance of the bootstrap estimates of standard error for the estimates may be affected by many factors, we observe that the bootstrap is still a practical method for estimating the sampling distribution of the estimate of intensity, whether or not one knows the underlying model of the process.

We observed that, if the original sample is not representative of the underlying pattern, the bootstrap estimates can be biased. SOLOW (1989) drew the same conclusion. For example, it is quite difficult to obtain representative samples in cluster point patterns. This fact can explain the significance of the main factor type of pattern and the interactions between type of pattern and number of events and between type of pattern and number of quadrats in the study region on the standard error. Table 1 shows that, in general, the precision of the bootstrap estimates is worse in cluster point patterns, that is, the standard error of the bootstrap estimates in cluster point patterns are, in general, bigger than estimates in CSR point patterns.

We noted some outliers for the estimates of standard error as we one can see the run numbers 25 and 29 (Table 1). These outliers can be explained as a peculiarity with the bootstrap method in sampled spatial point pattern. Since a bootstrap sample is randomly drawn with replacement from the original sample, some of the observations will be included more than once in each replication. For example, a particular bootstrap sample could be formed only by quadrats with large numbers of events (e.g. cluster). As a consequence, estimates from bootstrap samples can be considerably large.

Although the ideas behind the bootstrap are simple, elegant and powerful, its performance is dubious for estimating the intensity (and its standard error) of disease cases located in different geographical areas when sampling is done by selecting quadrats. Thus, the method must be evaluated in other types of point processes, such as those with events regularly distributed (e.g. simple inhibition and Markov point processes), described in CRESSIE (1993) and DIGGLE (1983). It is also necessary to perform an evaluation of bootstrap methods on other estimators of intensity, such as distance, areal and line transects, as described in UPTON and FINGLETON (1985). The use of bootstrap methods in other fields of spatial point patterns (e.g. to multivariate point pattern, tests of randomness) could also be investigated.

5 Conclusions

The simulations showed that the bootstrap estimates of the standard error and consequently, the confidence interval for spatial intensity depends on all the main factors, except for the number of bootstrap samples. Thus, in practice, there is no need to carry out bootstrap for constructing confidence regions for the spatial intensity, as the analytical estimator leads to results which can be obtained simplier without simulation. We expect that the results provided by this work may propitiate to the researcher some directions that can be useful in cases where they need to know quickly, and in a precise way, the number of disease cases in a geographical area, starting from a sample of case locations in a specific region.

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